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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,071	05/04/2006	Antonio Camargo	4705-0111PUS1	8916

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EXAMINER

MACFARLANE, STACEY NEE

ART UNIT	PAPER NUMBER
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1649

NOTIFICATION DATE	DELIVERY MODE
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11/13/2007

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/538,071	CAMARGO ET AL.	
	Examiner	Art Unit	
	Stacey MacFarlane	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 117-139 is/are pending in the application.
- 4a) Of the above claim(s) 119-125 and 127-139 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 117, 118 and 126 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 June 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/24/2007; 7/09/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Formal matters

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Election/Restrictions

2. Applicant's election with traverse of Group I, Claims 117-118 and 126 in the reply filed on October 12, 2007 is acknowledged. The traversal is based upon Applicant's assertion that the "special technical feature" that links the present claims is the finding that EOPA plays a role in brain development/function and thus that abnormality in EOPA expression is diagnostic of one or more of the several conditions recited in claim 117. This is not found persuasive for the reasons as follows. The expression "special technical feature" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions makes over the prior art. Whether a particular feature makes a contribution over the prior art, is considered with respect to novelty and inventive step. In the instant application, the only active step required, in order to practice the claimed method, comprises assessing the amount of EOPA protein as measured by an immunoassay using an antibody that specifically binds to EOPA, the amount of EOPA protein being indicative of a congenital disease of brain development, a disease resulting from tissue degeneration or schizophrenia. This inventive step does not make a contribution over the prior art. The Camargo reference (cited in the Paper

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filed September 13, 2007) teaches the assessment of the amount of EOPA protein by immunoassay and, thus, teaches the corresponding special technical feature of the claims. Therefore, there is no special technical feature over the prior art and the application lacks Unity of Invention under PCT Rule 13.1.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 119-125 and 127-139 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 12, 2007.

4. Claims 117, 118 and 126, in so far as they read upon the elected method for diagnosis comprising assessing the amount of EOPA protein, are under examination in the instant Office Action.

Claim Objections

5. Claim 117 is objected to for reciting non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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7. Claims 117, 118 and 126 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 117 is vague and indefinite in so far as it employs the term "Endooligopeptidase A (EOPA)" as a limitation. This term appears to be novel, and without a reference to a precise amino acid sequence identified by a proper SEQ ID NO: one cannot determine the metes and bounds of "Endooligopeptidase A (EOPA)". Moreover, because the instant specification does not identify that property or combination of properties which is unique to and, therefore, definitive of a "Endooligopeptidase A (EOPA)" or "EOPA protein", an artisan cannot determine if a compound which meets all of the other limitations of a claim would then be included or excluded from the claimed subject matter by the presence of this limitation.

9. Claim 117 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the definitive step that leads to diagnosis.

10. Claims 118 and 126 require the use of an antibody that specifically binds to EOPA, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 117, 118 and 126 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 117, 118 and 126 are directed to methods for the diagnosis of congenital diseases of brain development, of disease resulting from tissue degeneration in the brain, or of schizophrenia by measuring the amount of EOPA protein by immunoassay in brain tissue or cultured cells. The invention is based on hypothesis that the peptidase activity and/or non-proteolytic chaperone activity of EOPA influences the formation of active complexes that are important for cellular processes within the nervous system (Specification, paragraph 0058). As it is stated by Applicant, "The interaction of the EOPA with Lis1 and Disc1 is essential for the formation of the central nervous system during the embryogenesis, and for vital functions such as the intracellular transport, neuritogenesis, nuclear mobility, and plasticity of the nervous tissue. Interactions anomalies cause neurological diseases as the lissencephaly and the Miller-Diecker syndrome (Reiner et al., 1993; Cardoso et al., 2002). Recently, another pathology describing EOPA participation is the schizophrenia. Schizophrenic patients produce a truncated or mutant form of Disc1 that does not bind to EOPA, and this anomaly seems

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to be linked to the triggering of the disease (Ozeki et al., 2003; Taylor et al., 2003)".

However, the instant specification is not enabled for the method of diagnosis of congenital disorders based solely on an assessment of the amount of EOPA protein in brain or cultured cells, as currently presented, for the following reasons. The instant specification does not provide neither enough guidance for such method of determination of diagnosis, nor any working examples, which would show that the claimed method was successfully achieved, thus, requiring undue experimentation on part of one skilled in the art to discover how to practice Applicant's invention, as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention is the demonstration that EOPA protein is present in pluripotent neuronal stem cells and that it migrates to the ends of the neurites, suggesting a possible role for EOPA in the formation of cellular extensions or connections with other cells (¶ 0053) and that EOPA serves non-proteolytic functions, specifically, through coiled-coil domain interactions with other cytosolic proteins such as Lis1 and Disc1 (¶ 0062). As Applicant states, "The helical structure and its ability to interact with other proteins seem to be related to the nuclear and neuronal migration,

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suggesting an important function for this structure in the process of cellular movement, which occurs mainly during embryogenesis" (§ 0061).

The prior art recognizes that the Nudel protein (which Applicant has identified as being the same as the instantly claimed EOPA, see paragraph 0060) "binds multiple components ...that appear to determine the organization of the centrosome" and that "Nudel is a substrate for phosphorylation by cdk5, an important molecule for process extension and axon fasciculation" (see Ross and Walsh, Annual Review of Neuroscience 24: 1041-1070, 2001, specifically Figure 2 and page 1050). However, the reference teaches that one of the challenges to understanding Lis1 function is that the enzyme it encodes is ubiquitous (page 1047, first paragraph) and that the roles for EOPA/Nudel within the neuronal migration scheme are "tenuous at best" (page 1050, second paragraph).

With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification (see MPEP 2111 [R-1], which states that claims must be given their broadest reasonable interpretation

"During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to

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amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 51 (CCPA 1969)".

As such, the broadest reasonable interpretation of the claimed method is that it allows the diagnosis of any congenital disease of brain development or disease resulting from tissue degeneration in the brain or schizophrenia, merely by assessing the amount of EOPA protein in any sample obtained from brain of any subject/animal or even in any cultured cells via an immunoassay. Thus, the claims encompass the diagnosis of an unreasonable number of conditions caused by a broad range of unrelated pathologies, and the disclosure provides no nexus for the amount of EOPA protein levels to any pathological condition such that the skilled artisan would know how to diagnose. As opposed to the claims, what is disclosed about the claimed method is narrow: tissue-specific expression of EOPA in frog embryos was assessed by immunoassay, and homozygous deleterious mutations of the EOPA gene are non-viable and overexpression interferes with nervous system formation (specification ¶ 0064). No evidence of a correlation between levels of protein as assessed by immunoassay and any congenital disease of brain development, disease resulting from tissue degeneration in the brain, or schizophrenia has been put forth so that one of ordinary skill in the art would know how to practice the instantly claimed method.

While the skill level in the art is high, the level of predictability is low. As the Ross and Walsh reference (*Id*) indicates, the instantly claimed protein is associated with other proteins involved in neuronal migration processes, however the mechanistic

interactions and specific functions of the protein within these processes remains unknown. While it is not necessary that Applicant understands or discloses the mechanism by which the invention functions, in this case, in the absence of such an understanding, no extrapolation can be made of the results of an immunoassay for protein expression and a diagnosis of disease. Furthermore, the following reference teaches that much unpredictability remains within the art as to a definitive biomarker of the brain malformation disorders encompassed by the method (Caspi et al. The Journal of Biological Chemistry, 278(40): 38740-38748, October 2003). The Caspi reference teaches that the phenotypes produced by a single amino acid alteration in the EOPA/Nudel binding protein Lis1, leads to "unpredictable alterations in biochemical and cellular properties", implicating that "there are probably different biochemical and cellular mechanisms obstructed in each patient yielding the varied lissencephaly phenotypes" (title and abstract). Therefore, the state of the art at the time of filing indicated that even a known mutation, correlated to severe brain malformation is unpredictable with respect to assessing phenotype.

Applicant's invention is predicated on the finding within the art that EOPA protein interacts with Lis1 and/or Disc1. Applicant further extrapolates this result into a method for diagnosing developmental or degenerative diseases of the brain or schizophrenia based on the amount of EOPA protein as measured by immunoassay. Accordingly, it would appear that Applicant utilizes the findings of EOPA protein interactions, known in the art at the time of filing, and then presents an invitation to experiment and discover what role if any EOPA protein levels play in these brain diseases and, further, to

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correlate protein level expression a to definitive diagnosis of one of these diseases. Aside from claim 126, which recites, "an antibody that specifically binds to EOPA is used", the disclosure has not even provided active steps by which a skilled artisan would perform the method of diagnosis. For example, EOPA is an intracellular protein and the method reads upon diagnosis using a specific antibody in vivo, for which there is no enabling guidance or direction as to how one of ordinary skill in the art would assess EOPA protein levels in vivo.

The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc. v. Novo Nordisk*, 42 USPQ 2d 100, (CAFC 1997), the court held that: "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution.

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacey MacFarlane whose telephone number is (571) 270-3057. The examiner can normally be reached on M,W and ALT. F 6 am to 3 pm, T & R 5:30 am - 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.


Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Stacey MacFarlane
Examiner
Art Unit 1649

/SNM/


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PRIMARY EXAMINER